



# Toward Music Medicine: A Framework for Music Features and Alzheimer's Disease

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## Abstract

The incidence of Alzheimer's disease (AD) is rising rapidly, yet there aren't definitive diagnostic methods or effective interventions that can treat AD. Growing evidence shows that music can influence the brain in a positive way, but music has often been treated as an undifferentiated whole, rather than examining its individual acoustic features. This review bridges disconnected literatures to examine how isolated acoustic features can influence biological mechanisms related to AD. We first review non-AD evidence, spanning from neuroimaging, clinical disorders (anxiety, depression, and epilepsy), and cellular/rodent models, proposing that individual acoustic features may produce differential neural and physiological effects. We then synthesize AD-relevant biological pathways, including A $\beta$  and tau pathology, BDNF signaling, gene regulation via miR-132, and gamma oscillations. Finally, we propose three feature-pathway frameworks linking specific acoustic features to these biological pathways implied in AD. The evidence support levels of each pathway are asymmetrical, with rhythm showing the most direct evidence, while frameworks linking rhythm to BDNF and timbre to gamma oscillations remain more indirect and inferential. These frameworks are intended as a hypothetical conceptual map to guide future feature-isolation studies that aim toward developing more precise, non-pharmacological music interventions for AD.

## Keywords

Music medicine; acoustic feature; Alzheimer's disease; music-based-interventions; music therapy; precision medicine

## Introduction

Alzheimer's disease (AD) is a common neurodegenerative disease among older populations that affects 11% of the population over the age of 65 and nearly half of people aged 85 years and older (Gao et al., 2022). However, despite this prevalence, there are currently no definitive diagnostic tools or effective preventive and therapeutic interventions for AD (Gao et al., 2022).

At the same time, there is currently a growing interest in non-pharmacological approaches for AD, particularly music-based-interventions (MBI) (Rossetti, 2014). Broadly categorized into active music therapy and receptive music medicine (Huynh et al., 2026), MBIs, as well as acoustic stimuli like natural sounds, rhythmic drumming, and lullabies, have demonstrated cognitive, emotional, and social benefits across neurodegenerative populations (Chen et al., 2024; Navarro et al., 2023). Notably, many studies report that AD patients, who normally have challenges in memory recall, can still recognize familiar melodies (Cuddy and Duffin, 2005; Peck et al., 2016; Shankar, 2022; Chen et al., 2024). Some studies also report that listening to unfamiliar music can also enhance episodic memory recall in AD patients (Irish et al., 2006; Matziorinis and Koelsch, 2022; Chen et al., 2024).

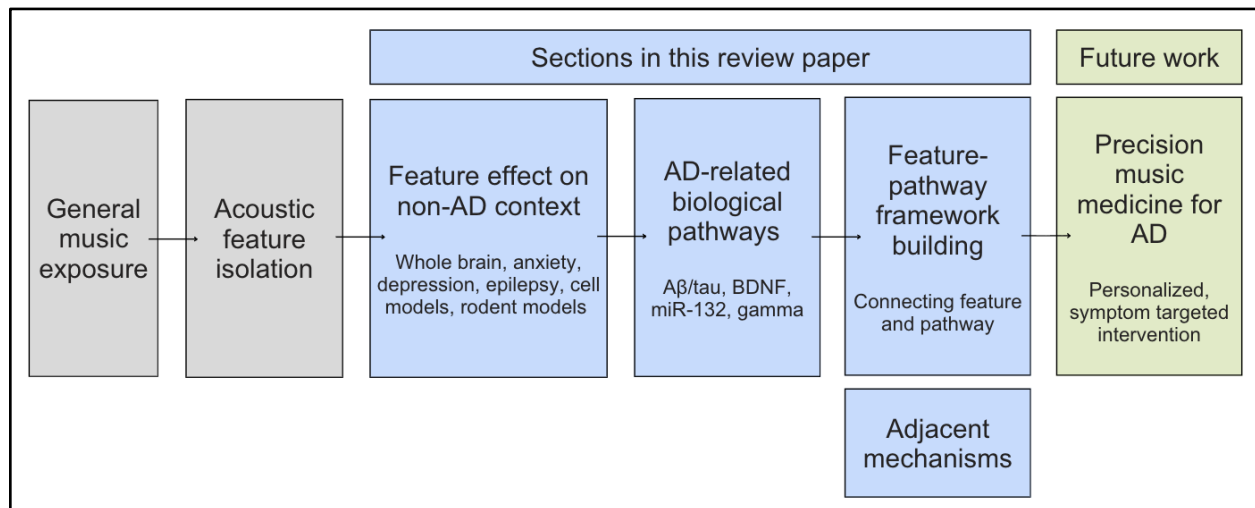
However, although recent research has evaluated the genomic, epigenetic, biological and chemical changes induced by music on the brain, most have treated music as an undifferentiated whole (Navarro et

al., 2021; Navarro et al., 2023; U et al., 2025), preventing the advancement of MBIs toward standardized, clinical prescription. Existing studies have generally categorized MBIs by intervention type or simply examined complete musical stimuli rather than individual musical features, masking the exact mechanisms at play (U et al., 2025; Gómez-Carballa et al., 2023).

However, music is, in fact, a multidimensional stimulus and can be divided into three fundamental categories: melody, harmony, and rhythm (Vuust et al., 2022). Melody refers to the pattern of pitched sounds; harmony refers to the combination of pitched sounds that forms chords; and rhythm refers to the structural arrangement of sounds (Vuust et al., 2022). The pitch itself is defined by fundamental frequencies. Timbre and tonality are also acoustic features of music, with timbre referring to the quality or color of the sound, and tonality referring to the organization of melody and harmony, giving music a certain direction (Vuust et al., 2022).

The emerging field of sensogenomics, the study of how sensory stimuli influence gene expression and the genome (Navarro et al., 2021) suggests that isolating these features is crucial. Overlapping yet distinct neural networks seem to process individual musical constituents (Vuust et al., 2022; Harding et al., 2025). Furthermore, several genes seem to be implicated in both music-related processes and AD (Navarro et al., 2023). To move toward prescribed, clinically standardized uses of music, we must move beyond asking if music works to how and which isolated features of music produce neurobiological effects.

In this review, we aim to bridge the disconnected literatures of feature-isolation research and AD molecular neuroscience by constructing feature-pathway frameworks that identify candidate relationships and highlight gaps for future experimental testing (Figure 1).



**Figure 1.** Conceptual framework and structural outline of the review. The review progresses from evidence that individual features of music can produce differential effects in non-AD contexts, to biological pathways implicated in AD, and finally to three proposed feature-pathway frameworks. An adjacent mechanism involving whole music exposure and miR-132 is considered separately because it does not isolate a specific acoustic feature. The overall framework identifies candidate relationships between specific acoustic features and AD-related biological mechanisms while distinguishing these hypotheses from broader whole music effects. The review may serve as a potential hypothesis map for future work related to developing precision music medicine for AD.

We will first look into how music and its specific features affect the brain in a non-AD context, investigating whether different acoustic features actually have differential effects. Then, the review will provide a

synthesis of current research on AD-related biological pathways. The specific acoustic features and AD-related pathways will be associated in a framework. To construct these frameworks, a literature search was conducted through Google Scholar using keywords including “acoustic features of music,” “AD,” and “music-based-interventions.” Studies were selected based on their relevance to at least one of these components: (1) the effects of specific acoustic features of music, (2) biological pathways related to AD, (3) clinical effects of music-based-interventions. Studies that isolated or quantified acoustic features, directly measured biological or clinical outcomes, or provided evidence connecting music exposure to AD-related pathways were prioritized. Because direct studies linking individual music features to AD-related biological pathways were limited, evidence from non-AD clinical populations, cellular and animal models, and related sensory stimulation studies were also considered when it provided relevant evidence. Studies examining the wider effect of music were utilized to establish a broader context, including the adjacent relationship between whole music exposure and miR-132, rather than as evidence for feature-specific framework. The three pathways were selected based on the availability of evidence connecting both sides of the framework: music features and AD-related biological pathways. Other AD mechanisms were excluded when relevant music-feature evidence was insufficient.

## Differential Biological Modulation in Non-AD Context

### **Whole Brain**

Before turning to AD-specific pathways, we first ask whether isolated features are indeed processed differentially in the brain through exploring non-AD evidence.

Alluri et al. (2011) scanned the participants’ brains with fMRI while they were listening to the *Adios Nonino*, a tango by Astor Piazzolla. Alluri and colleagues computationally extracted and selected six acoustic components that represented the main timbral, tonal, and rhythmic features of the piece. The team noted that each feature activated different, hardly overlapping regions of the brain. Timbral features activated mainly perceptual and default mode areas of the cerebrum, and cognitive areas of the cerebellum (Alluri et al., 2011). Timbral features also showed correlation with the temporal lobe, mostly when there were quick passages and complex melodies with several pitches and instruments being played (Alluri et al., 2011). On the other hand, tonal and rhythmic features engaged subcortical emotion-related structures as well as cognitive and somatomotor cerebrocortical areas (Alluri et al., 2011). These functional dissociations among acoustic features shown through computational audio analysis and brain imaging provide empirical support for the idea that individual features of music can be isolated and target specific neural regions.

Focusing specifically on rhythm, Grahn and Brett (2007) made participants reproduce different types of rhythmic sequences: metric simple (the rhythms are separated in integer ratio intervals, and the accents happen at regular intervals), metric complex (the rhythms are separated in integer ratio intervals like metric simple rhythm, but accents happen irregularly), and nonmetric rhythms (the rhythms are separated in non-integer ratio intervals, and accents happen irregularly). Participants reproduced metric simple rhythms more accurately, suggesting that integer ratio intervals and regular accent intervals may induce internal beat perception (Grahn & Brett, 2007). For rhythms with simple integer ratios, people often perceived a pulse (around 1.5–2.5 Hz) and spontaneously moved along (Harding et al., 2025). Neuroimaging (fMRI) further revealed that listening to metric simple rhythms increases activity across regions involved in both auditory and motor processing, such as the basal ganglia, anterior superior temporal gyri, left inferior frontal gyrus, and the pre-SMA/SMA (supplementary motor areas), more than the other rhythms, while areas like cerebellum and premotor cortex show similar activity level across all rhythm types (Grahn & Brett, 2007). These findings demonstrate that mathematically different rhythms both differently and similarly engage neural circuits related to movement.

Similar to rhythms, melodies can also be mathematically quantified through the ratio of distances between consecutive pitches, known as melodic intervals (Harding et al., 2025). Intervals based on simple ratios, such as a fifth, 3:2, generate stronger memory traces than intervals based on complex ratios, such as a tritone, 45:32 (Harding et al., 2025).

The mechanism behind how these different features produce differential neural effects could be explained by Neural Resonance Theory (NRT) (Harding et al., 2025). According to NRT, neural oscillations synchronize and resonate with external stimuli to form stable patterns (Harding et al., 2025). Furthermore, through attunement, neural circuits continuously adapt and align themselves to the environmental stimulus (in this case, musical patterns) over time, enabling the brain to process them more efficiently and flexibly (Harding et al., 2025).

In summary, as musical features, such as rhythm and melody, can be quantified, and neural circuits can synchronize themselves with the different musical stimulus via NRT, isolated musical features could predictably target and modulate specific brain networks.

## ***Clinical Disorders***

We now turn to clinical disorders and examine whether this feature-specific neural engagement translates to differential effects on disease-relevant symptoms.

### ***Anxiety***

Luo et al. (2025) investigated the effect of tonality (major and minor key) and timbre (violin and piano) on anxiety. Among the anxiety group, major-key violin music showed the greatest anxiety reduction effect, along with gamma-band alterations and engagement of prefrontal circuits (Luo et al., 2025). On the other hand, for the control group, minor-key piano music significantly reduced gamma waves (Luo et al., 2025). This suggests that acoustic features may differentially affect individuals with different clinical conditions.

Luo and colleagues suggest that this anxiety reduction effect on individuals reporting anxiety symptoms may have been due to violin timbre, which is shown to be rougher and has greater frequency density than piano. Auditory roughness can cognitively be perceived as a threat or salient cue, and this may have triggered defensive responses and captured attention, possibly helping alleviate anxiety symptoms by redirecting attention from internal thoughts that evoke anxiety (Luo et al., 2025).

This study by Luo et al. (2025) thus suggests how the specific physical and acoustic characteristics of timbre and tonality can induce anxiety-specific therapeutic effects.

### ***Depression***

Cheng et al. (2024) studied the effects of different music genres (light, classical, atonal composition, and rock music) using mice with chronic unpredictable mild stress (CUMS) (CUMS can create depression-like behaviors in mice). Exposure to light and classical music increased sucrose preference and reduced immobility time, suggesting an improvement of depression-like behaviors, while atonal composition and rock music did not show these effects (Cheng et al., 2024). This suggests that specific tonality, rhythm, and roughness constituting a genre were significant in inducing these antidepressant effects.

From a biochemical perspective, music shown to have antidepressant effects also showed enhanced Brain-Derived Neurotrophic Factor (BDNF) signaling, synaptic proteins, and neurogenesis (Cheng et al., 2024; Yeh et al., 2015).

Furthermore, on a neural-circuit level, these features seem to interact with cortical rhythms, especially gamma oscillations. Gamma oscillation and high gamma oscillations have emerged as biomarkers for major

depression, with therapeutic recovery in both human treatments and animal models being linked to gamma power alterations (Fitzgerald & Watson, 2018). In fact, many treatments, both pharmacological and non-pharmacological, alter gamma oscillations, and changes in gamma have been associated with recovery in animal models (Fitzgerald & Watson, 2018). Given that major-key violin music modulates gamma oscillations (Luo et al., 2025), and neural circuits resonate with external stimulus via NRT (Harding et al., 2025), it may be possible that specific acoustic features of music could alleviate depressive symptoms in a similar way pharmacological treatments do.

However, one confounding factor is that depression is not uniformly linked with a simple increase or decrease in gamma power. For instance, serotonergic drugs suppress gamma, while noradrenergic drugs increase gamma power (Fitzgerald & Watson, 2018). This divergence suggests that individual depressive states may be characterized by distinct circuit-level dysregulations, connecting to why certain patients respond to specific drugs while others do not (Fitzgerald & Watson, 2018). These findings again highlight the necessity of individualized music medicine that can be precisely targeted to the individual's unique profile.

## ***Epilepsy***

Štillová et al. (2021) investigated the effects of musical features on epileptiform discharge (ED) by playing Mozart's *Sonata for Two Pianos K. 448* and Haydn's *Symphony No. 94* to epileptic patients. The acoustic features of the pieces, the rhythmic, dynamic, and timbre musical features, were parameterized and analyzed (Štillová et al., 2021).

In general terms, listening to Mozart's piece decreased EDs by 32%, while listening to Haydn's piece increased EDs by 45% (Štillová et al., 2021). When discussing the beneficial effects of music, many theories propose an explanation with the activation of the cerebral reward system (Štillová et al., 2021). However, as patients did not report any significant preference to the compositions, it is unlikely that one specific composition caused a differential level in pleasure and thus a difference in the level of released dopamine (Štillová et al., 2021). Instead, the different physical features of each composition may have affected EDs through affecting brain oscillations (Štillová et al., 2021). Computational audio analysis also revealed that Mozart's K. 448 features a more harmonic spectrum, lower and more stable auditory roughness, and a higher long-term periodicity. These specific musical features, particularly the periodicity and repetition, may resonate with brain oscillations and suppress abnormal discharges (Štillová et al., 2021). Importantly, Štillová et al. (2021) noted that K. 545, another piece by Mozart also shown to have antiepileptic effect, shares similar spectrogram characteristics with K. 448. This structural resemblance strongly suggests that the antiepileptic effect may be driven by specific acoustic features (in this case, a group of specific elements) within a sound.

In addition, the acoustic elements that seemed to be correlated with decrease in EDs were different for men and women (Štillová et al., 2021). Men and women were each sensitive to different acoustic elements; for instance, men were sensitive to dissonance and high-frequency parts, while women were more sensitive to dynamics (Štillová et al., 2021). Although this research does not clearly show specifically which musical element leads to a decrease or increase in EDs, or rather if the change is an emergent outcome of several acoustic elements combined, it suggests that certain acoustic features can modulate brain activity and highlights the necessity of designing feature-optimized, sex-specific musical interventions for neurological disorders.

## ***Experimental Models***

### ***Cellular Models***

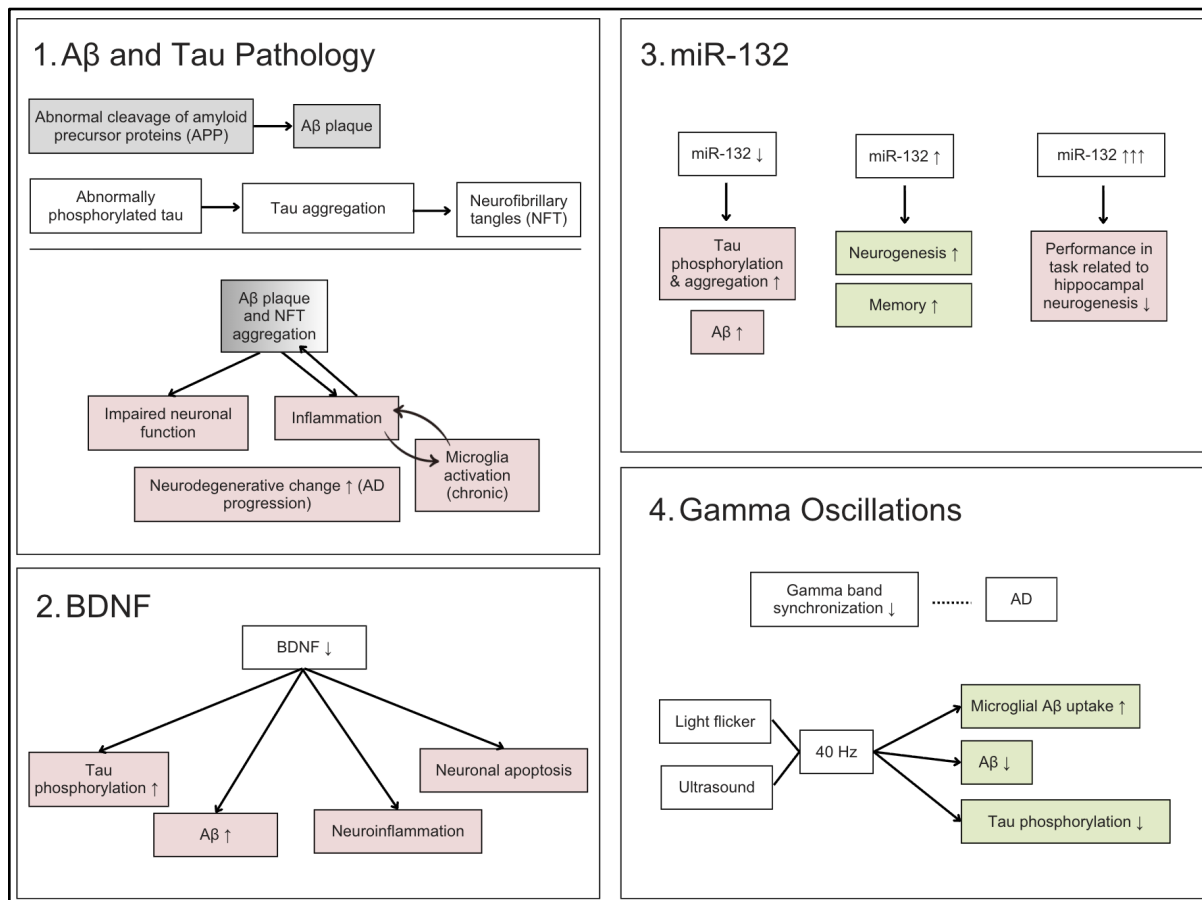
Experiments with cellular models have also shown how acoustic features of music can influence models that lack auditory systems. In a study by Ramírez-Rivera and Bernal (2019), AGS gastric cancer cells were exposed to metal and classical music. The study showed that proliferation of AGS gastric cancer cells increased in metal music (Ramírez-Rivera & Bernal, 2019). Music seems to also be able to induce changes in gene expression associated with apoptosis and cell-cycle control, while these changes are slightly different for each genre (Ramírez-Rivera & Bernal, 2019). Although the mechanisms are not completely understood yet, the frequencies and amplitudes composing the specific genre may have differentially affected gene expression, which in turn may have led to changes in proliferation of cells. Indeed, Brun and Exbrayat (2022) suggest that fluids in cells are sensitive to pressure changes, which can also be caused by sound waves. These studies suggest that some features of music, such as frequency and amplitude, can act as physical stimuli and affect cells, even without going through the auditory cognition process.

### ***Rodent models***

A study by Zhang et al. (2023) compared the effect of classical music (Mozart K. 448), white noise, and control (silence) in mice. While exposure to Mozart's K. 448 increased body weight, positively affected the composition of gut microbiota and immune responses, white noise had the opposite effect (Zhang et al., 2023). Although the specific elements constituting K. 448 was not the main focus of the study, this study shows how a very specific type of sound (white noise) can differentially modulate stress pathways and gut-brain axis function.

Together, evidence from neuroimaging, clinical studies, and cellular/rodent models suggests that music, a stimulus constituted of multiple sub-features, does not act uniformly; instead, the isolated features may engage distinct neural and molecular mechanisms. We now turn to the specific biological pathways implicated in AD, before asking whether these feature-specific effects observed in non-AD contexts can be extended to AD-related mechanisms.

## AD Related Pathways



**Figure 2.** Biological pathways implicated in Alzheimer's disease considered in this review. The diagram summarizes four pathways selected due to their relevance to both music-related research and AD biology: Aβ and tau pathology, BDNF, miR-132, and gamma oscillations. Arrows indicate the proposed direction of biological relationships discussed in the text. The red color represents negative outcomes that may be related to worsening of AD. The green color represents positive outcomes that may be related to potential improvement or prevention of neurodegenerative changes in AD. The figure summarizes AD mechanisms in current literature.

### Aβ and Tau Pathology

Broadly, AD pathology is characterized by the aggregation of two proteins, Aβ and tau (Gao et al., 2022). These proteins respectively form insoluble, extracellular Aβ plaques and intracellular neurofibrillary tangles (NFT) (Gao et al., 2022; Masters et al., 2015).

Aβ plaques form due to an abnormal cleavage of amyloid precursor proteins (APP) (Walker, 2020) (Figure 2). Normally, APP is cut by α-secretase and produces harmless fragments; however, when APP is processed by β-secretase and γ-secretase, amyloid beta peptides are released, eventually developing larger plaques (Walker, 2020). On the other hand, tau is a microtubule associated protein that is normally involved in stabilizing microtubules and promoting axonal growth (Wang & Mandelkow, 2015). It also has a low tendency to aggregate and form tangles, as it is highly soluble (Wang & Mandelkow, 2015). However, when tau becomes abnormally phosphorylated, the binding affinity of tau to microtubules decreases and

causes tau to be detached from microtubules (Wang & Mandelkow, 2015). An increase of these phosphorylated tau seems to be associated with an increase in tau aggregation, ultimately leading to the formation of NFT (Wang & Mandelkow, 2015).

The accumulation of A $\beta$  plaques and NFT can trigger inflammation and lead to neuronal death, contributing to the development of AD (Gao et al., 2022; Masters et al., 2015). The accumulation of A $\beta$  in the brain is considered as an early toxic event in AD pathogenesis, preceding more advanced neurodegenerative changes (Gómez-Carballa et al., 2023).

The main cause of AD seems to be the failure to remove A $\beta$  peptide from the brain tissue (Masters et al., 2015). However, the problem is that these pathways start a positive feedback relationship and worsen over time. Inflammation initiated by A $\beta$  plaques and NFT can activate microglia, impair neural function, and worsen the accumulation of A $\beta$  (Li et al., 2025). In addition, A $\beta$  and tau themselves also seem to be related. It is shown that reducing tau can lead to decreased A $\beta$  pathology and toxicity in mice (Hernandez-Rapp et al., 2016).

### ***BDNF***

Brain-Derived Neurotrophic Factor, BDNF, is one of the neurotrophic factors that is often discussed in music and AD-related literature. BDNF plays an important role in neuronal survival and growth, and regulates neuronal plasticity, which is important for learning and memory (Bathina & Das, 2015; Gao et al., 2022). Although the exact mechanisms are yet unknown, depletion of BDNF has been associated with tau phosphorylation, A $\beta$  accumulation, neuroinflammation, and neuronal apoptosis (Gao et al., 2022), which are all pathways involved in AD pathology (Figure 2). As AD progressed, BDNF levels in the brain, blood, and cerebrospinal fluid decreased, while an increase in serum levels of BDNF was associated with an improvement in cognitive functions among AD patients (Gao et al., 2022). Although most research related to BDNF and AD is correlational, increasing research suggests that there may be a link between BDNF and AD.

### ***miR-132***

MicroRNAs are non-coding RNAs that usually regulate gene expression at a post-transcriptional level, while some also play an important role in neural development, differentiation and maturation (M. Zhang & Bian, 2021). Among all the microRNAs, miR-132 is one of the most abundant in the brain (M. Zhang & Bian, 2021). Interestingly, miR-132 may be involved in the progression of both A $\beta$  and tau pathology, with the decrease in level of miR-132 also showing potential as a biomarker for AD (M. Zhang & Bian, 2021; Hernandez-Rapp et al., 2016; Smith et al., 2015; Walgrave et al., 2021).

In mice models, a deficiency in miR-132 led to increased expression, phosphorylation and aggregation of tau proteins, with miR-132 targeting tau mRNA to regulate its expression (Smith et al., 2015; Lau et al., 2013) (Figure 2). Beyond its role in tau regulation, miR-132 is also implicated in A $\beta$ . In a study by Hernandez-Rapp et al. (2016), genetically deleting miR-132 in triple transgenic mice increased A $\beta$  production and senile plaque deposition. This suggests that miR-132 may normally contribute to suppressing abnormal A $\beta$  metabolism.

Indeed, in a study by Walgrave et al. (2021), restoring miR-132 into the hippocampus of AD mice model improved neurogenesis and memory deficits. On the other hand, overexpression of miR-132 also led to worsened performance in a task related to adult hippocampal neurogenesis (Walgrave et al., 2021). It seems that miR-132 levels must be kept within a certain range, and that an abnormal increase or decrease can lead to progression of AD.

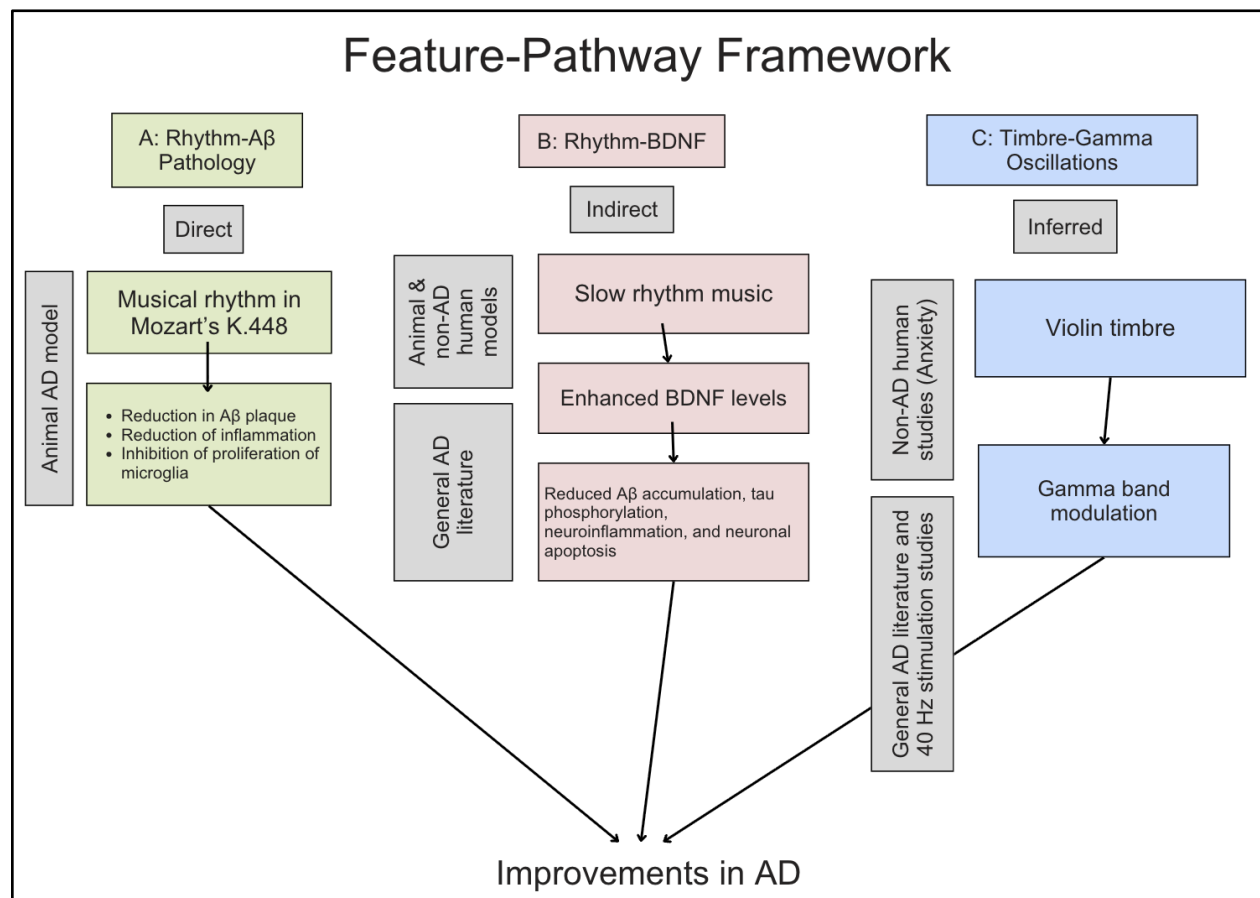
### ***Neural Oscillations***

Gamma oscillations are another pathway of interest, as their disruption is a prominent feature across many neurodegenerative diseases and thus may directly contribute to cognitive deficits observed in these conditions (Nimmrich et al., 2015).

Gamma oscillations are known to support long-term memory formation, attention, and working memory (Fell et al., 2002; Gruber et al., 1999, 2002; Kaiser et al., 2003; Jensen et al., 2007; Nimmrich et al., 2015). A loss of gamma band synchronization has been reported in AD, perhaps due to this important role gamma oscillations play in many cognitive functions (Stam et al., 2002; Nimmrich et al., 2015) (Figure 2).

This pathway has also been targeted as a therapeutic approach. Iaccarino et al. (2016) explored the usage of visual stimulation on driving gamma range oscillations by exposing mice to lights flickering at 40 Hz. They found that 40 Hz light flicker may create 40 Hz oscillations in the visual cortex (Iaccarino et al., 2016). 40 Hz flicker resulted in an increase in microglial A $\beta$  uptake, significantly reduced A $\beta$ 1-40 and A $\beta$ 1-42 levels, and reduced tau phosphorylation (Iaccarino et al., 2016). Interestingly, light flicker at other frequencies or random flicker did not significantly reduce A $\beta$  levels compared to controls (dark and light), suggesting that 40 Hz flicker may modulate gamma oscillations and start an overall neuroprotective response (Iaccarino et al., 2016). Similarly, Yi et al. (2026) observed reduced A $\beta$  plaque deposition and increased plaque related microglial activity in mice models after a transcranial ultrasound stimulation (TUS) at 40 Hz. Yi and colleagues also observed enhanced gamma oscillations in the hippocampus after the treatment, suggesting that external stimuli of 40 Hz may alter neural oscillations.

## Main Feature-Pathway-AD Frameworks



**Figure 3.** Proposed feature-pathway frameworks linking music-related stimuli with AD. The three feature-pathways frameworks are presented in descending order of evidentiary strength: Framework A, rhythm-A $\beta$  Pathology; Framework B, rhythm-BDNF; and Framework C, timbre-gamma oscillations. Gray boxes indicate the level and source of evidence supporting each specific link within the pathways. Framework A represents the most direct pathway, supported by an AD rodent model (APP/PS1 mice) that tested isolated musical rhythm. Framework B bridges evidence from animal and non-AD human models (showing music/rhythm induced BDNF enhancement) with general AD literature (linking BDNF to reduced A $\beta$ , tau phosphorylation, neuroinflammation, and neuronal apoptosis). Framework C is an inferred framework combining non-AD human studies on musical timbre and gamma modulation with general AD and 40 Hz stimulation literature. The arrows represent proposed or hypothesized relationships rather than established causal pathways.

### ***General Music and AD-Related Pathways***

Several research has shown that music as an undifferentiated whole engages A $\beta$ /tau relevant, BDNF, gene-regulatory, and gamma-oscillatory pathways.

This section attempts to narrow from general music exposure to specific feature-pathway frameworks. To the best of the author's knowledge, there aren't many studies experimentally testing the exact feature-pathway framework this review suggests. Thus, the frameworks are hypothetical and ordered from most direct evidence to most inferential, A, B, and C (Figure 3).

#### ***A. Rhythm-A $\beta$ Pathology-AD***

This framework connecting rhythmical features, A $\beta$  pathology, and AD is the one with the most direct evidence. Unlike the majority of studies investigating the effect of music on the brain, Li et al. (2025) tested the rhythm component of the widely used Mozart's K. 448. The musical notes in K. 448 were all changed to the same note (Middle C), while the original rhythm, tempo, dynamics, and timbre were preserved. Although there were some limitations in this study, it is the only study referenced in this paper that most resembles feature-isolation experiments. This edited extract was played to mice models (APP/PS1 mice) from 20:00 to 00:00, 4 hours every day for 6 months (Li et al., 2025). In order to obtain a better measurement of the potential effect of musical rhythm exposure on mice, the rhythm was played during mice's natural peak activity during dark phase, when mice's perception of auditory stimuli and responsiveness are normally enhanced. The study found a reduction in the area of A $\beta$  plaques in the hippocampus and enhanced performance on cognitive behavioral tests, such as the Morris Water Maze, after long-term musical rhythm exposure (Li et al., 2025).

Furthermore, an inhibition of abnormal proliferation of microglia in the hippocampus and reduction of inflammatory factors in the serum of AD mice were observed. As discussed in the previous section, an increase in A $\beta$  plaques may contribute to the development of AD (Gao et al., 2022). Abnormal proliferation of microglia, which can also be accelerated by the increase in A $\beta$  plaques, can contribute to further inflammation in the brain (Gao et al., 2022).

Thus, if listening to Mozart's K. 448 rhythm leads to a reduction in A $\beta$  plaques, inhibition of proliferation of microglia, and reduction of inflammation, this suggests that rhythm may potentially be able to slow neurodegeneration, or improve cognitive functions through the A $\beta$  pathology pathway.

Li et al. (2025) attempts to explain this mechanism of rhythm on A $\beta$  pathology by stating that music is a more ecological stimulus than the monotonous 40 Hz used in prior AD research, and that classical

compositions, including K. 448 has a unique 1/f rhythm spectrum that shares structural similarities with physiological rhythms in the body.

This proposal is worth sitting alongside a separate body of evidence on repetitive sensory stimulation and A $\beta$  pathology. Iaccarino et al. (2016), Yi et al. (2026), and Lv et al. (2025) each used different modes of stimulation: visual flicker in Iaccarino et al. (2016), ultrasound in Yi et al. (2026), and electrical in Lv et al. (2025). These different modes were all delivered at 40 Hz, and each showed a reduction in A $\beta$  plaque deposition and increase in microglial activity associated with plaque.

It is important to note that these findings should not be directly equated with the effects of musical rhythm. A 40 Hz stimulus repeats 40 times per second, whereas musical rhythm is generally measured in beats per minute and is usually at a slower temporal scale. For instance, a tempo of 120 beats per minute corresponds to only 2 beats per second. Furthermore, none of these three studies used music.

Nevertheless, the convergence of these studies raises a broader question of whether precisely structured repetitive stimulation, rather than specifically 40 Hz, may contribute to A $\beta$  and microglial responses. In this context, the repetitive temporal structure of music may be worth investigating as a potentially relevant feature, although the mechanism may differ from that of 40 Hz stimulation. Indeed, the relationship is hypothetical and would require experiments that directly manipulate musical rhythm while measuring gamma activity, A $\beta$  pathology, and microglial responses.

A similar idea of temporal structure has been proposed outside the AD literature. In the context of epileptic seizures, Štillová et al. (2021) proposed that the particularly high repetition rate and long-term periodicity of K. 448 may resonate with brain activity. Although this study concerns a different disorder and makes a different mechanistic claim, it provides an example of how temporal organization of musical stimulus may be considered biologically relevant. Together with findings of Li et al. (2025), these studies support the broader hypothesis that temporal structure may be an important property to investigate.

## ***B. Rhythm-BDNF-AD***

This framework connecting rhythm, BDNF, and AD is more indirect. Here, we attempt to bridge the two distinct links of studies: rhythm and BDNF with BDNF and AD.

Previous studies have shown that exposure to slow rhythm music (6 hours per day for 21 days) significantly enhanced BDNF levels in the hypothalamus of mice models (Angelucci et al., 2007). Similarly, listening to Mozart's K. 448 enhanced BDNF levels in the dorsal hippocampus CA3 and dentate gyrus, while the BDNF levels in dorsal hippocampus CA1 were not affected (Xing et al., 2016). Music seems to affect selective regions, and a change in BDNF levels seems to be correlated with enhanced spatial cognition ability, as measured with the Morris water maze task (Xing et al., 2016). BDNF may have affected hypothalamus activity by regulating glucose and energy metabolism of hypothalamus (Angelucci et al., 2007).

The systematic review by Kühlmann et al. (2018) suggests that higher BDNF levels and an enhanced propensity for neurogenesis and neuroplasticity in music-exposed rodents are patterns repetitively observed in multiple rodent studies. Although not specifically AD patients, an increase in serum BDNF levels after listening to Mozart's music for patients with mild cognitive impairment (Pecci et al., 2016) and young adults (Petekkaya et al., 2024) suggests that similar patterns are observed in both rodent models and humans.

Another strand of literature suggests that depletion of BDNF may be linked with A $\beta$  accumulation, tau phosphorylation, neuroinflammation and neuronal apoptosis (Gao et al., 2022). Connecting these two strands, it may be possible that listening to specific rhythm, such as slow rhythm music, can enhance BDNF

levels, which may in turn slow neurodegeneration in AD by either increasing neuroplasticity or preventing the accumulation of A $\beta$  plaques and NFT.

However, it is important to note that whether rhythm, or broadly music, directly leads to changes in BDNF levels is not entirely clear, as many studies tested the combined effect of music and exercise. For instance, although this was in a study related to depression, BDNF levels in human populations increased after participating in an activity combining music and exercise (Yeh et al., 2015). Physical exercise has also been shown to enhance BDNF levels and seems to have a similar effect on the brain as music (promoting synaptic protein expression and neurogenesis) (Cheng et al., 2024). It may be that music and exercise may be operating synergistically, with the interaction between music and exercise amplifying the overall impact (U et al., 2025).

### ***C. Timbre-Gamma Oscillations-AD***

This framework connecting timbre, gamma oscillations, and AD is inferred. As established in the section “Differential Biological Modulation in Non-AD Context,” timbral features and other features (tonal and rhythmic) seem to each engage different areas of the brain (Alluri et al., 2011). Auditory roughness, an aspect of timbre, engages a cascade of neural activity: initial high-gamma synchronization in the auditory cortex, limbic activation in the insula and amygdala, and finally the recruitment of parietal and prefrontal cortices (Arnal et al., 2019). Again, although this study was conducted to investigate the effect of music against anxiety, Luo et al.’s (2025) study is consistent with this pathway. Major-key violin timbre produced significant cortical activation, especially in the Brodmann areas 9 and 32 in the frontal lobe (Luo et al., 2025). This suggests that timbre’s roughness may recruit prefrontal circuits as part of its anxiety reducing effect.

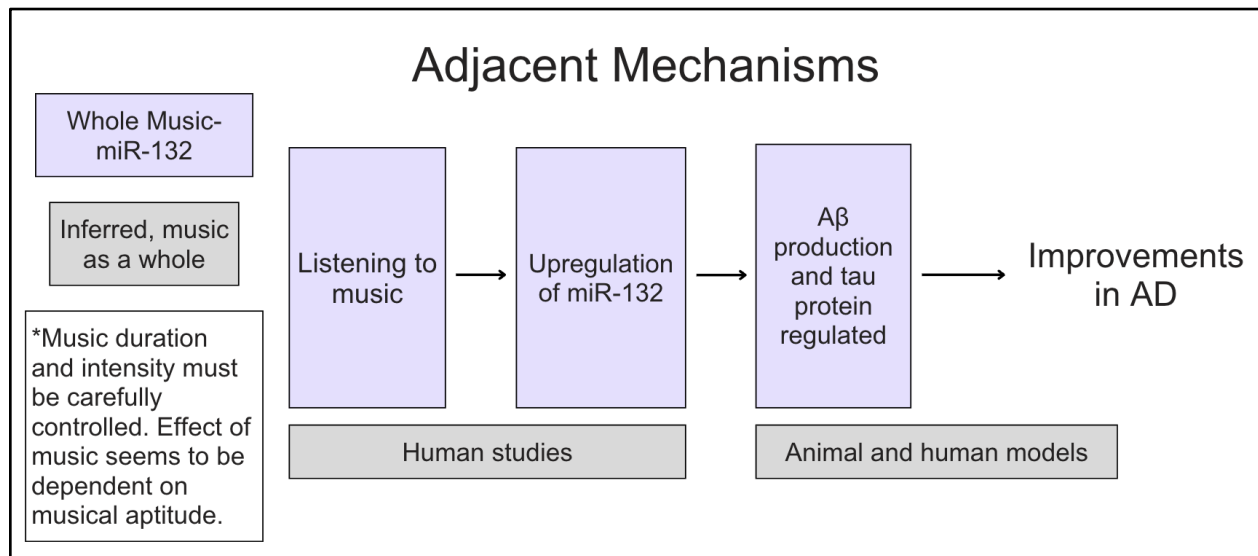
Importantly, this effect seems to be specific to the gamma band rather than the general property of neural oscillations. In the study by Luo et al. (2025), both beta and gamma bands were measured, but gamma activity showed more robust changes among the anxiety group. Granger causality analysis further suggested that the anxiety reduction previously linked with the prefrontal circuits is strongly associated with gamma-band connectivity (Luo et al., 2025). Luo et al. (2025) interpreted that gamma oscillations reflect emotion-cognition interactions and rapid information processing.

While musical timbre, specifically auditory roughness of violin, appears to influence gamma bands, the disruption of gamma oscillations is a prominent feature in many neurodegenerative diseases and may be related to cognitive deficits (Nimmrich et al., 2015). Indeed, several studies reported alterations in gamma oscillations, such as loss of gamma band synchronization, in AD (Nimmrich et al., 2015).

However, because the effect of timbre on gamma activity was observed in non-AD context (anxiety), the therapeutic potential of gamma modulation in AD relies on separate 40 Hz sensory stimulation research. These studies demonstrated that 40 Hz stimuli may be able to reduce A $\beta$  plaques and increase related microglial activity (Iaccarino et al., 2016; Yi et al., 2026; Lv et al., 2025).

Although there seems to be no studies that explicitly studied the effect of musical timbre on AD-related gamma alterations, we can infer from these separate lines of evidence that if specific timbral features can restore gamma oscillations, it may be possible that neurodegeneration in AD may be alleviated via pathways, such as A $\beta$  pathology. We emphasize once more that this framework remains hypothetical and needs empirical validation.

## Adjacent Mechanisms: Whole Music Exposure, miR-132, and AD



**Figure 4.** Proposed adjacent mechanism linking whole music exposure to AD via miR-132 regulation. Unlike the feature-isolated frameworks in Figure 3, this model considers music exposure as an undifferentiated whole. Gray boxes below the pathway indicate the underlying evidence sources, connecting human studies (demonstrating upregulated miR-132 expression following music exposure) with animal and human models (establishing miR-132's regulatory role in Aβ production and tau protein expression). The inset note emphasizes therapeutic considerations: optimal outcomes depend on precise control of music duration and intensity (avoiding cognitive deficits associated with overexpression of miR-132) and may be contingent upon individual musical aptitude.

Unlike the three feature-specific frameworks above, this section (Figure 4) considers evidence connecting whole music exposure with miR-132, a microRNA implicated in AD pathology. Although this section does not isolate a specific feature, it is included in the review as miR-132 seems to be one of the most mechanistically detailed and is relevant to the broader field of music medicine and sensogenomics. It is therefore presented as an adjacent mechanism rather than as a feature-pathway framework.

Nair et al. (2020) studied the effect of music listening on gene regulation and identified an upregulation of six microRNAs, including miR-132. Nair and colleagues' study in 2019 found a similar result in not only passive listening but also active musical performance, as observed by sequencing peripheral blood microRNA expressions in professional musicians after 2 hours of classical music performance.

miR-132 gained particular attention as it seems to play a critical role in regulating tau protein and Aβ production, important pathological pathways in AD (Nair et al., 2020). Hernandez-Rapp et al. (2016) found that miR-132 or its target Sirt1 can regulate Aβ production in humans, with miR-132 leading to downregulation of human Aβ-40 and Aβ-42 levels, while loss of miR-132 led to Aβ production, aggregation, and deposition in mice models. Smith et al. (2015) showed that miR-132 deficiency may also lead to increased tau expression, phosphorylation, and aggregation.

Furthermore, downregulation of miR-132 has been observed in the early and mid-stages of AD (Lau et al., 2013). The difference in miR-132 expression in AD was also stronger than other neuronal miRNAs,

suggesting that the downregulation of miR-132 may not be due to a simple cellular alteration in a diseased brain, but rather closer to being a pathological cause (Lau et al., 2013).

Considering this, modulating miR-132 levels through music exposure seems to show potential for AD treatment. However, there are two factors that must be taken into consideration.

First of all, while restoring miR-132 levels was shown to rescue hippocampus-dependent functions in AD mouse models, overexpression of the same microRNA seemed to be associated with worsening in cognitive tasks (Walgrave et al., 2021). This suggests that for music to be used therapeutically, the duration and intensity must be carefully controlled, as there seems to be a “goldilocks zone” for miR-132 levels.

Another factor is that this change in miR-132 was only observed in individuals shown to have high musical aptitude (Nair et al., 2020). This suggests that there could be genetic or epigenetic differences due to prior musical experience among musically apt individuals that may differentially interact with the miR-132 pathway. This is an important consideration as each individual has different levels of musical aptitude, and the effect of this aptitude on miR-132 regulation cannot be clearly outlined yet.

## **Discussion**

Constructing these feature-pathway frameworks demonstrates a clear asymmetry in the strength of supporting evidence. Framework A is the only one that directly tested isolated acoustic features (rhythm) against AD pathology outcomes in real animal models. Framework B, on the other hand, bridges two well-supported links, music’s effect on BDNF and BDNF’s effect on AD pathology. However, this gap is complicated by the frequent confounding of music and exercise in existing literature. Framework C is the most inferential, with the link between timbre, gamma oscillations, and AD not clearly defined. Timbre’s effect on gamma oscillations is established in non-AD context, while gamma stimulation’s effect on AD pathology is established in non-musical context. While all three frameworks partially depend on studies based on entire music (not isolated features), the adjacent mechanism is solely based on studies that treat music as an undifferentiated stimulus. This asymmetry itself indicates where feature-isolated AD research should prioritize moving forward.

### ***Limitations and Future Directions***

There are several limitations and confounds in this review that should be further studied.

#### ***Musical Aptitude Confound***

A recurring confound across this review is musical aptitude. Several changes by music were only observed in individuals that reported high musical aptitude (Nair et al., 2020; Grahn & Brett, 2007), and many studies, taking account of this confound, designed their population to only have individuals with musical experience or only have individuals with no prior musical training experience (Luo et al., 2025; Alluri et al., 2011). Furthermore, although musical aptitude seems to greatly influence the therapeutic effects of music, the concept of musical aptitude itself is not clearly defined and is often self-reported (Navarro et al., 2021). This collectively suggests that many of the pathway’s effects discussed in this review may not uniformly generalize across all music listeners. A clearer definition and measurement method of musical aptitude must be first established in order for future research to effectively study the effect of musical aptitude on music listening and AD.

#### ***Music-Exercise Confound***

Similarly, Framework B’s rhythm-BDNF link is complicated by studies that combine music listening with exercise, making it unclear whether rhythm or other musical features are sufficient alone to elevate BDNF.

Studies should investigate the effect of musical feature alone (rhythm) on BDNF levels, while removing exercise components or keeping it as a control.

### ***Animal to Human Translation***

Many studies related to music, brain, and AD, often use rodent models. This is likely because rodent models enable the usage of more invasive experiments, such as directly stimulating the brain with electrical stimulus (Lv et al., 2025), analyzing gut-microbiota (Z. Zhang et al., 2023), and directly analyzing the BDNF levels in the hippocampus (Xing et al., 2016). However, rodents and humans are indeed different species, and results obtained in rodent models may not directly translate to humans. In addition, music may not be perceived the same way as humans in animal models, and many studies suggest that music may lack ethological relevance for animals (U et al., 2025). All three frameworks involve studies based on rodent models, and future research should study whether the same patterns also appear in humans.

### ***Dose-Response Relationship***

The “goldilocks zone” observed for miR-132, where restoration and overexpression led to adverse effects (Walgrave et al., 2021) underscores a broader limitation: no study in this review systematically varied the duration or intensity of musical exposure to establish a dose-response relationship. There were attempts to quantify acoustic features using mathematical ratios in rhythm (Grahn & Brett, 2007) and melody (Harding et al., 2025). Further work should quantify and parametrize these acoustic features and outline the effects on AD-related pathways. One important element that should also be quantified and tested is duration of music exposure. Many studies discussed in this review had varying exposure durations, ranging from minutes to months. However, exposure time seems to greatly affect the outcome, as in a study by Petekkaya et al. (2024), notable changes in serum BDNF only appeared after 15 days.

Furthermore, continuing with the musical aptitude confound, each individual may have different outcomes after listening to the same musical stimulus as individuals have different musical backgrounds. The influence of musical aptitude levels on this dose-response relationship should also be further studied.

### ***Further Acoustic Feature-Specific Relationships***

Again, a limitation is that many studies simply treat or generalize all classical music together, while each music and composer may have different acoustic compositions. Simply comparing music of different genres or composers isn't sufficient to reveal the mechanism behind music and AD-related pathways.

Another major gap is the feature-pathway link for tonality. Although tonality was shown to differentially affect anxiety-related symptoms (Luo et al., 2025), it lacks evidence that can be linked to AD-related pathways. Future research should thus test the effect of tonality on AD context, perhaps by using AD mice models.

### ***Depression and AD***

Another interesting line of future research is exploring how depression and AD may be related to each other. Depression and AD were discussed separately in this review, but the two seem to engage in similar pathways, such as BDNF (Cheng et al., 2024; Gao et al., 2022). Depression also seems to exacerbate AD pathology through lactate-dependent activation of potassium channel Kv1.3, promoting A $\beta$ -containing exosome spreading (Liu et al., 2025). The further mechanistic connection between depression and AD should be studied. The feature-specific effects of music could be able to simultaneously affect both conditions.

### ***Implications***

Although it is not directly related to AD, the sex-specific responses observed by Štillová et al. (2021) as well as the differential responses by anxiety groups and control groups in Luo et al. (2025) suggest that a single intervention is unlikely to suit all individuals. Even for pharmacological treatments, each individual responds to each drug differently (Fitzgerald & Watson, 2018). Music should move away from the general idea that all music can impact individuals in the same way; each acoustic component that constitutes a musical stimuli seems to have the potential to differentially help alleviate neurological disorders, such as AD. Further research finding the optimal features on an individual level may be able to support the movement toward prescribed, standardized music medicine (Cheng et al., 2024; Štillová et al., 2021). We hope that the feature-pathway frameworks proposed in this review could serve as a starting point for future research aiming towards these individualized, symptom-targeted prescriptions.

## Conclusion

This review suggests that music's individual acoustic features engage distinct biological pathways that may be relevant to AD. By connecting feature-isolation research and AD neuroscience, we constructed three feature-pathway frameworks (A-C) connecting rhythm and timbre to A $\beta$  and tau pathology, BDNF, and gamma oscillations. Alongside these feature-specific pathways, we also highlighted an adjacent mechanism involving whole music exposure and miR-132 regulation. These pathways each have different levels of evidence support, and this asymmetry suggests where future feature-specific research should prioritize moving forward. While several confounds, including musical aptitude and a heavy reliance on rodent models, limit how far these frameworks can be generalized, the convergence of evidence across neuroimaging, clinical studies, cellular and animal models suggests that this topic is worth pursuing further. Indeed, the therapeutic potential of music depends on understanding the exact mechanisms behind it: which acoustic feature actually did the work. As the field moves toward more personalized, prescribed music medicine, the feature-pathway framework proposed in this review serves as a conceptual starting point for future research by clarifying what can be inferred from current evidence and highlighting empirical gaps.

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